AD-A067 832 SCHOOL OF AEROSPACE MEDICINE BROOKS AFB TEX F/G 6/1
SERUM LIPOPROTEINS: CURRENT CONCEPTS OF METABOLISM AND RELATION--ETC(U)
MAR 79 D A CLARK

UNCLASSIFIED SAM-TR-79-10 NL

OF
AD
A067832

END
DATE
FILMED
6-79
DDC

REVIEW 2-79

LEVEL II

AEROMEDICAL REVIEW

SERUM LIPOPROTEINS: CURRENT CONCEPTS OF METABOLISM AND RELATIONSHIP TO HYPERLIPIDEMIAS

Dale A. Clark, Ph.D.

March 1979

USAF School of Aerospace Medicine
Aerospace Medical Division (AFSC)
Brooks Air Force Base, Texas 78235

NOTICES

This review was submitted by personnel of the Clinical Pathology Branch, Clinical Sciences Division, USAF School of Aerospace Medicine, Aerospace Medical Division, AFSC, Brooks Air Force Base, Texas, under job order 7755-18-02.

When U.S. Government drawings, specifications, or other data are used for any purpose other than a definitely related Government procurement operation, the Government thereby incurs no responsibility nor any obligation whatsoever; and the fact that the Government may have formulated, furnished, or in any way supplied the said drawings, specifications, or other data is not to be regarded by implication or otherwise, or in any manner licensing the holder or any other person or corporation, or conveying any rights or permission to manufacture, use, or sell any patented invention that may in any way be related thereto.

This review has been reviewed by the Information Office (OI) and is releasable to the National Technical Information Service (NTIS). At NTIS, it will be available to the general public, including foreign nations.

This technical report has been [illegible] for publication.

[illegible]
Project Scientist

[illegible]
Lt Col, USAF, MC
Chief, Clinical Sciences Div
Commander

SECURITY CLASSIFICATION OF THIS PAGE (When Data Entered)

REPORT DOCUMENTATION PAGE

READ INSTRUCTIONS BEFORE COMPLETING FORM

1. REPORT NUMBER: Aeromedical Review 2-79
2. GOVT ACCESSION NO.:
3. RECIPIENT'S CATALOG NUMBER: (9)

4. TITLE (and Subtitle): (6) SERUM LIPOPROTEINS: CURRENT CONCEPTS OF METABOLISM AND RELATIONSHIP TO HYPERLIPIDEMIAS
5. TYPE OF REPORT & PERIOD COVERED: Interim rept. Jan 1978—Jan 1979
6. PERFORMING ORG. REPORT NUMBER: (14) SAM—TR—79-10
7. AUTHOR(s): (10) Dale A. Clark, Ph.D.
8. CONTRACT OR GRANT NUMBER(s): SAM-REVIEW-2-79
9. PERFORMING ORGANIZATION NAME AND ADDRESS: USAF School of Aerospace Medicine (NGP), Aerospace Medical Division (AFSC), Brooks Air Force Base, Texas 78235
10. PROGRAM ELEMENT, PROJECT, TASK AREA & WORK UNIT NUMBERS: 62202F (7) 7755-18-02
11. CONTROLLING OFFICE NAME AND ADDRESS: USAF School of Aerospace Medicine (NGP), Aerospace Medical Division (AFSC), Brooks Air Force Base, Texas 78235
12. REPORT DATE: (11) March 1979
13. NUMBER OF PAGES: 13
14. MONITORING AGENCY NAME & ADDRESS (if different from Controlling Office): (12) 17 p.
15. SECURITY CLASS. (of this report): UNCLASSIFIED
15a. DECLASSIFICATION/DOWNGRADING SCHEDULE:

16. DISTRIBUTION STATEMENT (of this Report)

Approved for public release; distribution unlimited.

17. DISTRIBUTION STATEMENT (of the abstract entered in Block 20, if different from Report)

18. SUPPLEMENTARY NOTES

19. KEY WORDS (Continue on reverse side if necessary and identify by block number)

Lipoproteins, metabolism
Atherosclerosis
Heart disease
Cholesterol transport in serum
Hyperlipoproteinemias

20. ABSTRACT (Continue on reverse side if necessary and identify by block number)

This review summarizes current (1978) understanding of the interconversions of serum lipoproteins and the hyperlipoproteinemias associated with failure at specific points in the sequence. The different roles played by the low- and high-density lipoproteins in the transportation of cholesterol through the serum to and from peripheral tissues are discussed. Possible mechanisms for the effect of high-density lipoproteins in protecting against atherosclerosis are reviewed. Levels of various serum lipids and lipoproteins can be

DD FORM 1 JAN 73 1473 EDITION OF 1 NOV 65 IS OBSOLETE

UNCLASSIFIED

SECURITY CLASSIFICATION OF THIS PAGE (When Data Entered)

317 000

useful indicators of the causative metabolic defects or dietary problems associated with hyperlipidemias.

SERUM LIPOPROTEINS: CURRENT CONCEPTS OF METABOLISM AND RELATIONSHIP TO HYPERLIPIDEMIAS

FUNCTION AND CLASSIFICATION OF LIPOPROTEINS

To survive and to perform, the human organism must have energy available to use whenever required. Since food is ingested at intervals rather than continuously, the organism must have the capability of storing energy supplies when they are in excess and recalling them for use when required later. This need is met in part by the storage of excess fat in adipose tissue and by the conversion of excess carbohydrate into fatty acids which may be converted into triglycerides and stored in the adipose tissue. This storage system requires the transport of large amounts of lipids through the serum. In general, however, lipids such as cholesterol and the triglycerides which contain long chain fatty acids are rather insoluble in water. They therefore must be incorporated into complexes which effect their solubilization. This solubilization is accomplished by the combination of certain proteins, the apoproteins, with lipids such as cholesterol, triglycerides, and phospholipids, to form a complex macromolecule known as a lipoprotein.

The lipoproteins are sufficiently soluble in water to successfully transport the insoluble lipids through the aqueous serum. Current understanding of the interrelationship among these different serum lipoproteins and their lipid components is discussed in the following paragraphs.

The lipoproteins that circulate in the serum are divided into three major classes (in addition to chylomicrons). The common designations of these entities (19), their densities, and their separation by electrophoresis and the ultracentrifuge are listed in Table 1.

In Table 2 the components of these different lipoprotein classes are shown, listing each component percentage of the total weight of the complex (19). The density of the lipoprotein complex is a function of the relative proportions of lipid and of protein; the more protein, the greater the density. Conversely, the greater the proportion of lipid, the lower the density of the lipoprotein.

The protein components of the lipoproteins, when separated from their lipids, are referred to as the apoproteins. At least 11 are known (22) although the metabolic significance of some of these is uncertain. The apoproteins are part of an outer layer surrounding the central lipid core of the lipoproteins (18) which normally have a globular form as they circulate in serum.

TABLE 1. CLASSIFICATIONS OF LIPOPROTEINS

Basis of designation	Designation		
Current usage	HDL (high-density lipoprotein)	VLDL (very low-density lipoprotein)	LDL (low-density lipoprotein)
Electrophoresis	Alpha	Pre-beta	Beta
Ultracentrifuge	1.2	20-400	0-12
Density	$1.063 \leq d \leq 1.20$	$d \leq 1.006$	$1.006 \leq d \leq 1.063$

TABLE 2. LIPOPROTEIN COMPOSITION, LISTING COMPONENTS AS PERCENT OF THE WEIGHT OF THE LIPOPROTEINS[a]

	Cholesterol	Triglyceride	Phospho-lipid	Protein
Chylomicrons	7	84	7	2
VLDL	20	51	19	8
LDL	45	11	22	21
HDL	17	8	22	50

[a]Percentages sum to 100 (except for round-off errors) across horizontal lines. Sums of vertical columns are meaningful only if the quantity of each lipoprotein species in each serum is considered.

The chylomicrons consist primarily of triglyceride. They originate from the intestinal wall where digested fat is absorbed and resynthesized into triglycerides. The predominately triglyceride composition of the chylomicrons reflects their role as the primary mechanism for transport of triglycerides absorbed from the intestine, i.e., exogenous triglycerides (24). The very low-density lipoproteins (VLDL) are approximately 50% triglyceride by weight. Biosynthesized primarily by the liver, although partially by

the intestine, they serve the function of carrying triglyceride from the point of origin to the peripheral tissues. Because of their mainly hepatic origin, the VLDL ordinarily transport primarily endogenous triglycerides. The low-density lipoproteins (LDL) are formed by stepwise delipidation and remodeling of the VLDL in the plasma (6). Since these lipoproteins are approximately 50% cholesterol by weight, they play a predominant role in the transporting of cholesterol to the peripheral tissues (24). In contrast, the high-density lipoproteins (HDL) have a smaller percentage composition of cholesterol and triglyceride. They originate in the liver and supply certain proteins required in the sequential conversion of other lipoproteins (20). In addition, HDL may act as a scavenger, picking up cholesterol in the peripheral tissues and returning it to the liver for disposition (9).

INTERRELATIONSHIPS AMONG THE LIPOPROTEINS

Although there are sequential metabolic interrelationships among the chylomicrons, the VLDL and the LDL (20, 24), these interrelationships are not direct interconversions of one lipoprotein into another but are more like a succession of remodelings. Both the lipid composition and the protein composition undergo some changes, although in some respects these changes are like variations on a central theme. For example, apo B, the chief protein obtained when LDL is delipidated, is part of the VLDL when it is secreted and remains with the macromolecule (6) throughout the sequential conversions of VLDL into intermediate-density lipoprotein (15) and finally into LDL. As this sequence proceeds, the proportion of the apo C decreases, and the proportion of apo E varies with the stage of delipidation (20). The proportion of triglyceride decreases while the proportion of cholesterol increases. These relationships are presented diagrammatically in Figure 1.

In the capillary beds of extrahepatic tissue, the chylomicrons lose much of their triglyceride to the tissue cells. The mechanism (6) involves the enzyme lipoprotein lipase which is present on the walls of the capillaries. This enzyme is activated by one of the apoproteins, C-II, acquired from the high-density lipoprotein. In consequence of this activation, the triglyceride in the chylomicrons is hydrolyzed and the fatty acids are picked up by the tissue cells. The liver picks up the remnant of the chylomicrons remaining after depletion of much of their triglyceride (24) as well as about one-third of the chylomicrons, which escape metabolism in the capillaries of peripheral tissues (12). The subsequent metabolic sequence in the liver is not clear, but various components may be utilized or reassembled to form other lipoproteins.

The VLDL are formed primarily in the liver, but some are made by the intestine. The chief protein, apo B, is conserved (15) during subsequent interconversions that produce the LDL. The VLDL function is to transport triglyceride from the site or origin to the peripheral tissue. In that process lipoprotein lipase is activated by C-II protein supplied by the HDL and plays the same role as in the case of the removal of triglyceride

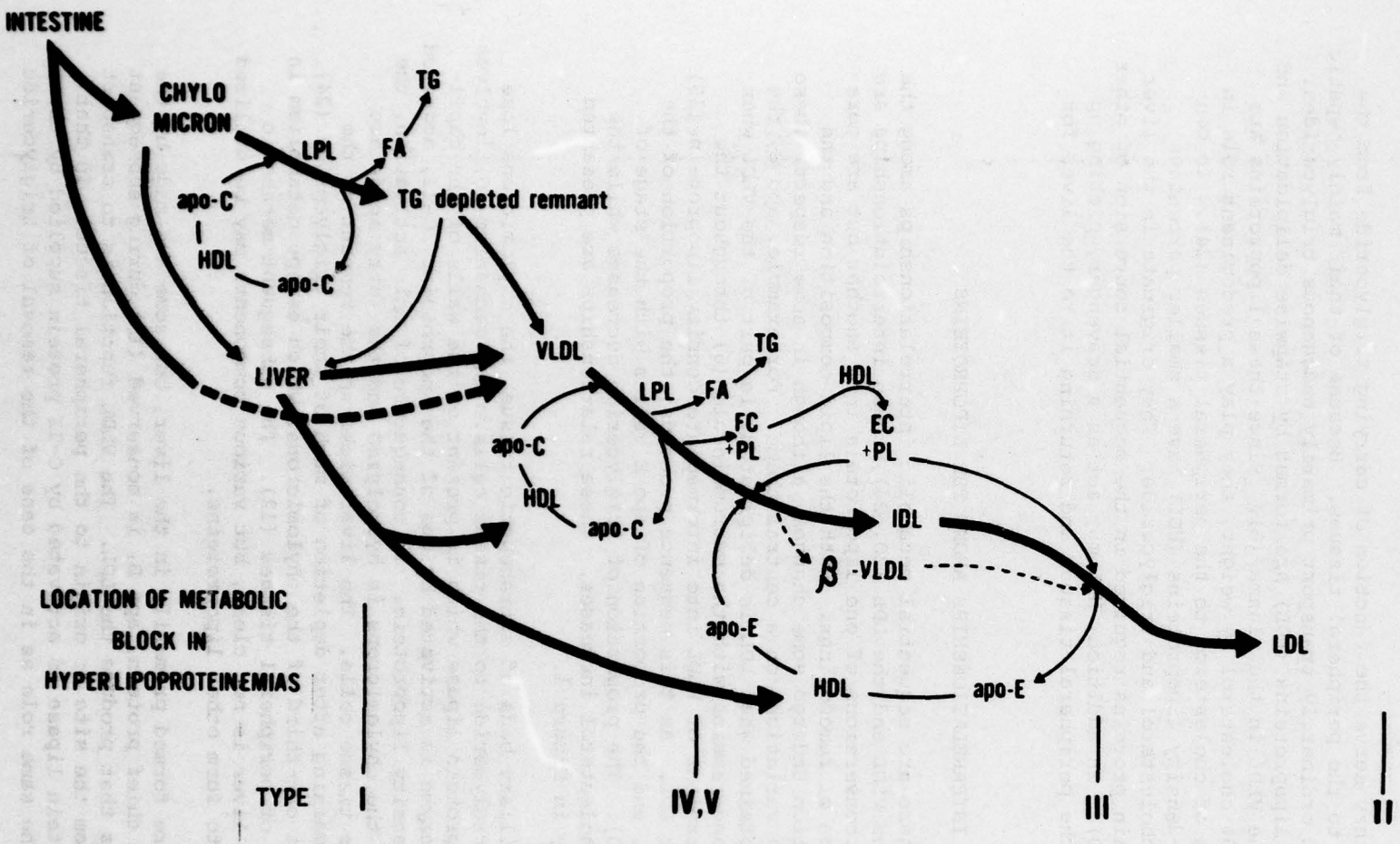

Figure 1. Schematic outline of lipoprotein interactions and relationships to hyperlipidemias. Nomenclature: EC - esterified cholesterol; FA - fatty acids; FC - free cholesterol; HDL - high-density lipoproteins; IDL - intermediate-density lipoproteins; LDL - low-density lipoproteins; LPL - lipoprotein lipase; PL - phospholipids; TG - triglycerides; VLDL - very low-density lipoproteins

from the chylomicrons. The triglycerides of the VLDL are hydrolyzed and the fatty acids are made available to the tissue cells (6). Some of the C-II protein required to activate the lipoprotein lipase is freed concomitantly, and some phospholipid and cholesterol (mostly free?) are transferred to HDL. This process of stepwise delipidation leads to the formation of the intermediate-density lipoproteins (IDL) (6). These may be a group of partially delipidated VLDL on the way to LDL. One such intermediate, B-VLDL (the "floating beta" lipoprotein), accumulates in the serum of individuals with Type III hyperlipoproteinemia. Its formation may be by a pathway separate from that by which the bulk of the IDL (20) is formed although both pathways may be utilized in normal persons. The further conversion of IDL to LDL apparently requires the binding of apo E either to the remnant protein or at the site of conversion of the remnant (12). With conversion of the remnant, apo E is released to HDL.

The LDL thus formed function to transport cholesterol to the peripheral tissues. Studies by Goldstein and Brown (10) have demonstrated that LDL enter human fibroblasts through either high-affinity binding sites on the cells or by a nonspecific ingestion of lipoprotein during pinocytosis (bulk pinocytosis). The mechanisms by which the lipoproteins are internalized after high-affinity binding are not clear (20). However, these mechanisms are of more than academic interest. Cholesterol entering the cell by the low-affinity (bulk pinocytosis) sites does not affect the metabolically active cellular pool of cholesterol, whereas cholesterol entering via the high-affinity sites does affect that pool (4). Cholesterol entering via high-affinity sites eventually finds its way to the lysosomes where the lysosomal enzymes hydrolyze the cholesterol esters to free cholesterol. These events are diagrammed in Figure 2. The free cholesterol functions in several ways (4): It inhibits the cholesterol synthesis by the cells; it depresses the LDL binding sites; and it stimulates the esterification of the free cholesterol. Various enzymes act upon those protein portions of the LDL that enter the cells and form various polypeptide remnants, which are broadly characterized as trichloroacetic acid (TCA) soluble products. Presumably, these peptides enter into catabolic pathways comparable to those followed by various other polypeptides and amino acids.

The binding of LDL at high-affinity sites in cultures of fibroblasts has been shown to be relatively specific (10). Although HDL can be bound at such sites and can inhibit binding of the LDL, affinity for HDL is less (5). Brown and Goldstein (4) suggested that HDL might protect against atherosclerosis by blocking the binding of LDL to endothelial cells or smooth muscle cells at injury sites in arterial walls. This attractive theory is supported by the demonstration that high ratios of HDL:LDL in cell cultures will decrease the binding of LDL and lessen the increase of the cholesterol level within the incubated cells (14, 20).

Such findings suggest that elevated levels of HDL could inhibit the formation of atherosclerotic plaques and may explain the inverse correlation of disease with serum HDL levels (16).

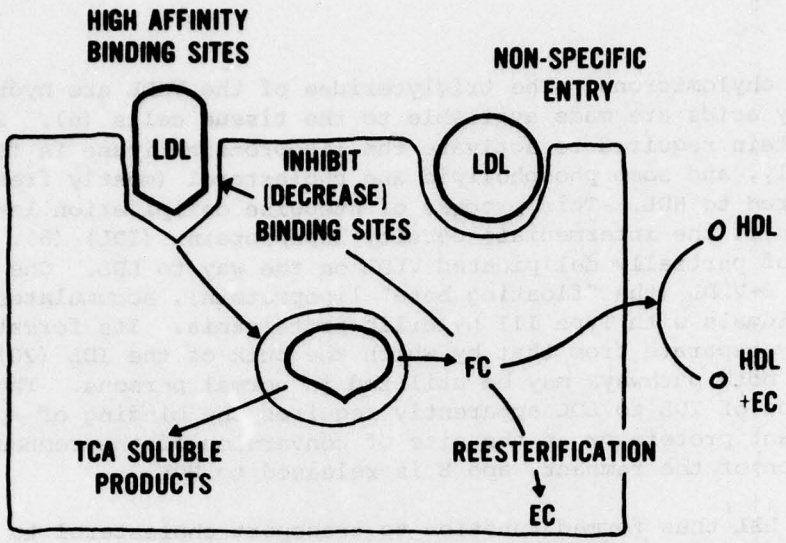

Figure 2. Internalization and cellular disposition of low-density lipoproteins. For the meaning of acronyms, see Figure 1 legend.

Prevention of plaque formation is one aspect of the relationships of HDL to decreased risk of heart disease. Another is implicit in the role of HDL as a scavenger of cholesterol (9).

After serving whatever functions may be required for the cell and the cell wall, a certain amount of cholesterol is apparently either surplus to the needs of the cell or cast off as detritus or cellular debris. This cholesterol and some phospholipid are picked up by the HDL which transports the cholesterol to the liver for further disposition or disposal (9). This role of the HDL is intimately related to the function of apo-A-I, one of the A-proteins, which activates the enzyme lecithin-cholesterol acyltransferase (LCAT). LCAT catalyzes the transfer of a fatty acid from a lecithin molecule to a molecule of free cholesterol, producing a molecule of esterified cholesterol. The resulting change in the polarity of the cholesterol molecule apparently causes the cholesterol esters to migrate from the surface of the HDL into the central lipid core (12). This process may underlie two facets of HDL metabolism--the conversion of the nascent HDL molecules into the normal globular form of serum HDL and the pickup of cholesterol from cells or plaques. The action of LCAT on the free cholesterol in the nascent HDL discs forms cholesterol esters which, when internalized, may cause the discs to swell into the normal globular shape of HDL (6). The pickup of cholesterol from cells is related to LCAT through the process of converting free cholesterol at the cell surface into cholesterol esters that would tend to enter the HDL molecule and be carried back to the liver (9). This mechanism could also account for the possible lytic role of the HDL in removing cholesterol from atherosclerotic plaques.

Bondjers and Bjorkerud (3) have reported that HDL mediates the solubilization of cholesterol from arterial tissue of atherosclerotic rabbits. Although this process requires hydrolysis of cholesterol esters in the plaque, the HDL may be a crucial factor in carrying the cholesterol away from the plaque. This is an attractive hypothesis, which may prove to be a key to understanding atherosclerosis (11). The process by which the liver removes cholesterol from HDL is unknown, but liver action is the main pathway for removal of cholesterol esters from HDL (24). Recently, Schwartz et al. (23) reported that free cholesterol of HDL is the favored substrate for the secretion of biliary cholesterol in man. However, LDL cholesterol was also efficiently utilized for this purpose. The latter observation fits with the ready transfer of cholesterol and phospholipids among the various lipoproteins (24). Preferential utilization of HDL cholesterol for secretion by the liver is an observation that adds credence to the scavenger role of HDL.

HDL AS A PREDICTOR OF RISK OF CARDIOVASCULAR DISEASE

HDL cholesterol has come to be recognized as a more efficient predictor of risk of cardiovascular disease (CVD) (14) than cholesterol. In contrast to total cholesterol and LDL cholesterol, however, levels of HDL cholesterol are inversely related to the risk of CVD (16). This fact has been known since early work by Barr et al. (1) and extensively studied in relation to the gonadal hormones (8, 25). The relative immunity of young women to atherosclerotic heart disease was associated with the finding of higher levels of cholesterol in their HDL fraction than in men. When this relationship was translated into a prediction of risk of heart disease and related to the newer understanding of the function of the HDL, levels of HDL cholesterol took on new significance (16). A wave of reports (5, 11, 17, 21, 26) on the importance of HDL-cholesterol has resulted, and interest continues to grow.

Data from the Framingham study (11), presented in Table 3, show that risk of CVD rises varies inversely with the HDL cholesterol level. Interestingly, the risk for males and females is the same when calculated on the basis of HDL cholesterol levels.

The Framingham population on whom the data in Table 3 were obtained are an older group. Ages range from 49 to 82. Since this group is not comparable to the Air Force pilot population, it is uncertain how the HDL cholesterol levels in USAF pilots will correlate with CVD. Nevertheless, the importance of the possible risk prediction is so great that measurement of HDL cholesterol in pilots must be vigorously pursued to determine what correlation exists.

If the current understanding of the roles assigned to HDL is correct, it seems reasonable that pilots with a high level of HDL cholesterol throughout their adult life should have decreased risk of cardiovascular disease. Data bearing on this hypothesis are being collected.

TABLE 3. FRAMINGHAM STUDY (11) DATA FOR INCIDENCE[a] OF CORONARY HEART DISEASE AS A FUNCTION OF HDL-CHOLESTEROL LEVEL

	HDL Level						
	<25	25-34	35-44	45-54	55-64	65-74	75+
Men	176.5	100.0	104.5	51.0	59.7	25.0	--
Women	--	164.2	54.5	49.2	39.7	13.9	20.1

[a]Figures given are incidence rate per 1000 subjects. Some variations in rate may result from small number of incidents in certain categories.

RELATIONSHIP TO HYPERLIPOPROTEINEMIAS

The Fredrickson classifications of hyperlipoproteinemias (2, 7, 13) and their associated deficiencies in the lipoprotein transport mechanism are indicated in Figure 1 and summarized in Table 4. Type I hyperlipoproteinemia is characterized by the presence of large amounts of chylomicrons in the serum. Since the associated abnormality is a deficiency of lipoprotein lipase, chylomicrons are not cleared rapidly from serum. When the levels of cholesterol and triglyceride in the serum are measured, only the triglyceride level is elevated. This elevation is not associated with a rise in the VLDL, but is attributed to the increased level of chylomicrons. After standing, a creamy layer on top of a relatively clear serum is usually seen. In Type IV hyperlipoproteinemia, the serum triglyceride level is also increased; however, in this case the deficiency is in the conversion of the VLDL to LDL so that the level of the VLDL is increased markedly. Since lipoprotein lipase is not deficient, there is not an accumulation of chylomicrons. The elevated triglyceride is accounted for by the elevated VLDL. In this case, the serum will appear milky because of the presence of the large amounts of VLDL. This milky appearance will persist when the serum stands, but there will be no separation of a creamy layer on top because the chylomicrons are absent. In Type V hyperlipoproteinemia, however, there are increased levels of triglyceride associated with elevated levels of both VLDL and chylomicrons. This serum, on standing, will have a milky appearance and a creamy layer on top.

In Type III hyperlipoproteinemia, there is a metabolic failure to metabolize one of the products of partial delipidation of the VLDL. In consequence there is an accumulation of this so-called B-VLDL in the serum.

This lipoprotein has electrophoretic mobility approximating that of the beta fraction but has the density of the VLDL. Consequently, when the VLDL lipoproteins are separated out, they will be found on electrophoresis

TABLE 4. GENERAL CHARACTERISTICS OF HYPERLIPOPROTEINEMIAS

Type	Abnormality	Appearance of refrigerated serum after standing	Levels of serum lipids/lipoproteins		
			Triglycerides	Cholesterol	Lipoproteins
I	Deficient lipoprotein lipase	Creamy layer over clear serum	Elevated	Usually some rise	Elevated chylomicrons
II-A	Dietary (excess cholesterol)	Clear	Normal	Elevated	Elevated LDL
II-B	Hereditary (plus excess fat and cholesterol)	Slightly milky, no creamy layer	Elevated	Elevated	Elevated LDL and VLDL
III	Abnormal VLDL (β-VLDL)	Cloudy, milky	Elevated	Elevated	Presence of an IDL that floats with VLDL but migrates as beta on electrophoresis (floating beta, or broad beta)
IV	Often dietary (carbohydrate, fat)	Milky, but no creamy layer	Elevated	Perhaps some rise	Elevated VLDL
V	Hereditary multiple hyperlipidemias	Creamy layer over milky serum	Elevated	Elevated	Elevated chylomicrons and VLDL, maybe LDL

to contain a fraction which migrates with the beta. This so-called "floating beta" fraction gives rise to the broad beta pattern seen on electrophoresis of the lipoproteins from the individuals who have this particular hyperlipidemia.

In Type II hyperlipidemia the LDL and the associated cholesterol are present in increased concentration. If only the LDL are increased, then the classification is Type II-A; however, both LDL and VLDL and its associated triglyceride are found to be increased in some cases and are designated Type II-B. In individuals who have Type II-A hyperlipidemia, the serum will be clear; since VLDL are not elevated, the serum will not have a milky appearance. However, serum from individuals having Type II-B hyperlipidemia will be milky because VLDL levels are elevated. Distinguishing this hyperlipidemia from Type III and Type IV by the appearance of the serum alone may lead to erroneous conclusions. However, if the cholesterol and triglyceride levels are also known, a fairly reliable estimate of the type of hyperlipidemia can be made. In Type IV, in which the serum is milky, the triglyceride will be elevated; but the cholesterol level will usually be normal or slightly elevated. In contrast, in Type II-B, the serum cholesterol level should be markedly elevated and the triglyceride and VLDL levels should be moderately elevated. In Type III, the LDL and cholesterol levels may be normal or only slightly elevated, but the triglyceride levels are markedly elevated.

These generalizations are often compromised by multiple abnormalities and confusing causative factors in many cases of hyperlipidemias. Such cases require more studies to clarify the abnormality. However, the extra studies required to relate the abnormal lipid levels to the different types of hyperlipoproteinemias should help to establish the metabolic causes of the hyperlipidemia and to assist in guiding the medical management of the patient.

SUMMARY AND PERSPECTIVE

The most important facts about lipoprotein metabolism that are clinically important to the flight surgeon center around the association of cardiovascular disease (CVD) with elevated levels of cholesterol and low-density lipoproteins (LDL) and low levels of high-density lipoproteins (HDL). CVD apparently results from LDL levels that are too high, or HDL levels that are too low, or a combination of these. This simplistic statement embodies many details and mechanisms, and emphasizes the current understanding of the association of LDL with delivery of cholesterol to nonhepatic tissues and the reverse transport of cholesterol to the liver by HDL. The Fredrickson classification of hyperlipoproteinemias is a way of relating the stages of lipoprotein metabolism affected in a given hyperlipidemic patient to the medical management of that patient. Such classification should assist in identifying appropriate therapeutic steps.

Caution and an alertness to change are indicated, however, because the generalities expressed in this review reflect the overall current state of

understanding in a rapidly changing field. The simplified relationships presented are based on details of metabolism of the various lipoproteins that are complex, controversial, and not well understood. Consequently, it is not yet certain how the metabolism of each apoprotein and its associated lipids contributes to the inhibition or development of CVD. The current intense research in these areas probably means that changes in interpretations may occur, but offers hope that the pace of significant progress will soon lead to a clear understanding of how better to assess and treat lipid abnormalities that lead to heart disease.

REFERENCES

1. Barr, D. P., E. M. Russ, and H. A. Eder. Protein-lipid relationships in human plasma. II. In atherosclerosis and related conditions. Am J Med 11:480-493 (1951).

2. Beaumont, J. L., et al. Classification of hyperlipidaemias and hyperlipoproteinemias. Bull WHO 43:891-915 (1970).

3. Bondjers, G., and S. Bjorkerud. Arterial repair and atherosclerosis after mechanical injury. VI. Cholesterol elimination in vitro from experimental atherosclerotic lesions. Exp Mol Pathol 26:341-349 (1977).

4. Brown, M. S., and J. L. Goldstein. Receptor mediated control of cholesterol metabolism. Science 191:150-154 (1976).

5. Carlson, L. A., and M. Ericsson. Quantitative and qualitative serum lipoprotein analysis. Part 1. Studies in healthy men and women. Atherosclerosis 21:417-433 (1975).

6. Eisenberg, S., and R. I. Levy. Lipoprotein metabolism. Adv Lipid Res 13:1-89 (1975).

7. Fredrickson, D. S., R. I. Levy, and R. S. Lees. Fat transport in lipoproteins - An integrated approach to mechanisms and disorders. N Engl J Med 276:34-44, 94-103, 148-156, 215-225, 273-281 (1967).

8. Furman, R. H., et al. The influence of androgens, estrogens, and related steroids on serum lipids and lipoproteins. Am J Med 24:80-97 (1958).

9. Glomset, J. A. The plasma lecithin: Acyltransferase reaction. J Lipid Res 9:155-167 (1968).

10. Goldstein, J. L., and M. S. Brown. The low-density lipoprotein pathway and its relation to atherosclerosis. Annu Rev Biochem 46:897-930 (1977).

11. Gordon, T., et al. High density lipoprotein as a protective factor against coronary heart disease. Am J Med 62:707-714 (1977).

12. Havel, R. J. New frontiers on the relationships of lipids, lipoproteins, and the arterial wall in cardiovascular disease. A Symposium of the Extension Division, University of California, on Metabolism of Lipoproteins in Humans and Other Mammals, Jan 1978.

13. Havel, R. J. Classification of the hyperlipidemias. Annu Rev Med 28:195-209 (1977).

14. Koschinsky, T., T. E. Carew, and D. Steinberg. Effects of high density lipoprotein (HDL) on low density lipoprotein (LDL) metabolism by pig smooth muscle cells. Circulation, Supp II:273 (1975).

15. Levy, R. I., D. W. Bilheimer, and S. Eisenberg. The structure and metabolism of chylomicrons and very low density lipoproteins (VLDL), pp. 3-17. In Biochemical Soc. Symposia No. 33, New York: Academic Press, 1971.

16. Miller, G. J., and N. E. Miller. Plasma high-density lipoprotein concentration and development of ischaemic heart disease. Lancet 1:16-19 (1975).

17. Miller, N. E., et al. The tromso heart study. High density lipoproteins and coronary heart disease: A prospective case control study. Lancet 1:965-967 (1977).

18. Morrisett, J. D., R. L. Jackson, and A. M. Gotto, Jr. Lipoproteins: Structure and function. Annu Rev Biochem 44:183-207 (1975).

19. Oncley, J. L., and N. R. Harvie. Lipoproteins--a current perspective of methods and concepts. Proc Nat Acad Sci 64:1107-1118 (1969).

20. Osborne, J. C., Jr., and H. B. Brewer, Jr. The plasma lipoproteins. Adv Protein Chem 31:253-337 (1977).

21. Rhoads, G. G., C. L. Gulbrandsen, and A. Kagan. Serum lipoproteins and coronary heart disease in a population study of Hawaii Japanese men. N Engl J Med 294:293-298 (1976).

22. Scanu, A. M., C. Edelstein, and P. Keim. Serum lipoproteins, 2d ed., Vol. 1, pp. 317-391. In F. W. Putnam (ed.). Plasma proteins. New York: Academic Press, 1975.

23. Schwartz, C. C., et al. Preferential utilization of free cholesterol from high density lipoproteins for biliary cholesterol secretion in man. Science 200:62-64 (1978).

24. Smith, L. C., H. J. Pownall, and A. M. Gotto, Jr. The plasma lipoproteins: Structure and metabolism. Annu Rev Biochem 47:751-777 (1978).

25. Stamler, J., et al. Effectiveness of estrogens for therapy of myocardial infarction in middle-aged men. JAMA 183:632-638 (1963).

26. Wood, P. D., et al. The distribution of plasma lipoproteins in middle-aged male runners. Metabolism 25:1249-1257 (1976).